

REMARKS

Claims 1-63 were pending. Claims 5 and 23 have been amended to clarify the invention. Therefore, claims 1-63 are pending. No new matter has been added.

Applicants note with appreciation that the Examiner has found claims 1-63 to be free of the prior art.

Rejection of Claims 1-63 under 35 U.S.C. § 112, first paragraph

Claims 1-63 were rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner "the specification, while being enabling for non-heterocyclic substituted creatine derivatives does not reasonable provide enablement for heterocyclic substituted creatine derivatives."

Without acquiescing to the Examiner's rejection, Applicants respectfully submit that this rejection no longer pertains to the claims as amended. Therefore, Applicants respectfully request that this rejection of claims 1-63 under 35 U.S.C. § 112, first paragraph be withdrawn.

SUMMARY

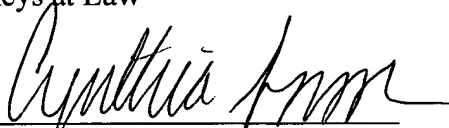
Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The amendments made to the claims are not related to any issues of patentability.

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call Elizabeth A. Hanley, Esq. at (617) 227-7400.

Date: January 29, 2003

LAHIVE & COCKFIELD, LLP
Attorneys at Law

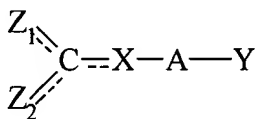
By



Cynthia M. Soroos
Reg. No. P53,623
28 State Street
Boston, MA 02109
(617) 227-7400
(617) 742-4214

Marked Up Version of Claims to Show Changes Made

5. [Amended] The method of claim 1, wherein said creatine compound has the formula:



and pharmaceutically acceptable salts thereof, wherein:

a) Y is selected from the group consisting of: -CO₂H, -NHOH, -NO₂, -SO₃H, -C(=O)NHSO₂J and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, C₁-C₆ straight chain alkyl, C₃-C₆ branched alkyl, C₂-C₆ alkenyl, C₃-C₆ branched alkenyl, and aryl;

b) A is selected from the group consisting of: C, CH, C₁-C₅alkyl, C₂-C₅alkenyl, C₂-C₅alkynyl, and C₁-C₅ alkoyl chain, each having 0-2 substituents which are selected independently from the group consisting of:

1) K, where K is selected from the group consisting of: C₁-C₆ straight alkyl, C₂-C₆ straight alkenyl, C₁-C₆ straight alkoyl, C₃-C₆ branched alkyl, C₃-C₆ branched alkenyl, and C₄-C₆ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

2) an aryl group selected from the group consisting of: a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: -CH₂L and -COCH₂L where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy; and

3) -NH-M, wherein M is selected from the group consisting of: hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkoyl, C₃-C₄ branched alkyl, C₃-C₄ branched alkenyl, and C₄ branched alkoyl;

c) X is selected from the group consisting of NR_1 , CHR_1 , CR_1 , O and S, wherein R_1 is selected from the group consisting of:

- 1) hydrogen;
- 2) K where K is selected from the group consisting of: C_1 - C_6 straight alkyl, C_2 - C_6 straight alkenyl, C_1 - C_6 straight alkoyl, C_3 - C_6 branched alkyl, C_3 - C_6 branched alkenyl, and C_4 - C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;
- 3) an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-\text{CH}_2\text{L}$ and $-\text{COCH}_2\text{L}$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;
- 4) a C_5 - C_9 a-amino-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;
- 5) a C_5 - C_9 a-amino-w-aza-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon; and
- 6) a C_5 - C_9 a-amino-w-thia-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

d) Z_1 and Z_2 are chosen independently from the group consisting of: $=\text{O}$, $-\text{NHR}_2$, $-\text{CH}_2\text{R}_2$, $-\text{NR}_2\text{OH}$; wherein Z_1 and Z_2 may not both be $=\text{O}$ and wherein R_2 is selected from the group consisting of:

- 1) hydrogen;
- 2) K, where K is selected from the group consisting of: C_1 - C_6 straight alkyl; C_2 - C_6 straight alkenyl, C_1 - C_6 straight alkoyl, C_3 - C_6 branched alkyl, C_3 - C_6 branched alkenyl, and C_4 - C_6 branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-\text{CH}_2\text{L}$ and $-\text{COCH}_2\text{L}$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a $\text{C}_4\text{-C}_8$ α -amino-carboxylic acid attached via the α -carbon;

5) B, wherein B is selected from the group consisting of: $-\text{CO}_2\text{H}$, $-\text{NHOH}$, $-\text{SO}_3\text{H}$, $-\text{NO}_2$, $\text{OP}(=\text{O})(\text{OH})(\text{OJ})$ and $-\text{P}(=\text{O})(\text{OH})(\text{OJ})$, wherein J is selected from the group consisting of: hydrogen, $\text{C}_1\text{-C}_6$ straight alkyl, $\text{C}_3\text{-C}_6$ branched alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_6$ branched alkenyl, and aryl, wherein B is optionally connected to the nitrogen via a linker selected from the group consisting of: $\text{C}_1\text{-C}_2$ alkyl, C_2 alkenyl, and $\text{C}_1\text{-C}_2$ alkoyl;

6) $-\text{D-E}$, wherein D is selected from the group consisting of: $\text{C}_1\text{-C}_3$ straight alkyl, C_3 branched alkyl, $\text{C}_2\text{-C}_3$ straight alkenyl, C_3 branched alkenyl, $\text{C}_1\text{-C}_3$ straight alkoyl, aryl and aroyl; and E is selected from the group consisting of: $-(\text{P}(\text{O})_3)_n\text{NMP}$, where n is 0-2 and NMP is ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-\text{[P}(=\text{O})(\text{OCH}_3)(\text{O})]_m\text{-Q}$, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; $-\text{[P}(=\text{O})(\text{OH})(\text{CH}_2)]_m\text{-Q}$, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chosen independently from the group consisting of: Cl, Br, epoxy, acetoxy, $-\text{OG}$, $-\text{C}(=\text{O})\text{G}$, and $-\text{CO}_2\text{G}$, where G is independently selected from the group consisting of: $\text{C}_1\text{-C}_6$ straight alkyl, $\text{C}_2\text{-C}_6$ straight alkenyl, $\text{C}_1\text{-C}_6$ straight alkoyl, $\text{C}_3\text{-C}_6$ branched alkyl, $\text{C}_3\text{-C}_6$ branched alkenyl, $\text{C}_4\text{-C}_6$ branched alkoyl, wherein E may be attached to any point to D, and if D is alkyl or alkenyl, D may be connected at either or both ends by an amide linkage; and

7) $-\text{E}$, wherein E is selected from the group consisting of: $-(\text{P}(\text{O})_3)_n\text{NMP}$, where n is 0-2 and NMP is a ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-\text{[P}(=\text{O})(\text{OCH}_3)(\text{O})]_m\text{-Q}$, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; $-\text{[P}(=\text{O})(\text{OH})(\text{CH}_2)]_m\text{-Q}$, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3

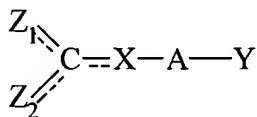
substituents chose independently from the group consisting of: C₁, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO=G, where G is independently selected from the group consisting of: C₁-C₆ straight alkyl, C₂-C₆ straight alkenyl, C₁-C₆ straight alkoyl, C₃-C₆ branched alkyl, C₃-C₆ branched alkenyl, C₄-C₆ branched alkoyl; and if E is aryl, E may be connected by an amide linkage;

e) if R₁ and at least one R₂ group are present, R₁ may be connected by a single or double bond to an R₂ group to form a cycle of 5 to 7 members;

f) if two R₂ groups are present, they may be connected by a single or a double bond to form a cycle of 4 to 7 members; and

g) if R₁ is present and Z₁ or Z₂ is selected from the group consisting of -NHR₂, -CH₂R₂ and -NR₂OH, then R₁ may be connected by a single or double bond to the carbon or nitrogen of either Z₁ or Z₂ to form a cycle of 4 to 7 members.

23. [Amended] The method of claim 19, wherein said creatine compound has the formula:



and pharmaceutically acceptable salts thereof, wherein:

a) Y is selected from the group consisting of: -CO₂H, -NHOH, -NO₂, -SO₃H, -C(=O)NHSO₂J and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, C₁-C₆ straight chain alkyl, C₃-C₆ branched alkyl, C₂-C₆ alkenyl, C₃-C₆ branched alkenyl, and aryl;

b) A is selected from the group consisting of: C, CH, C₁-C₅alkyl, C₂-C₅alkenyl, C₂-C₅alkynyl, and C₁-C₅ alkoyl chain, each having 0-2 substituents which are selected independently from the group consisting of:

1) K, where K is selected from the group consisting of: C₁-C₆ straight alkyl, C₂-C₆ straight alkenyl, C₁-C₆ straight alkoyl, C₃-C₆ branched alkyl, C₃-C₆ branched alkenyl, and C₄-C₆ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

2) an aryl group selected from the group consisting of: a 1-2 ring carbocycle ~~and a 1-2 ring heterocycle~~, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: -CH₂L and -COCH₂L where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy; and

3) -NH-M, wherein M is selected from the group consisting of: hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkoyl, C₃-C₄ branched alkyl, C₃-C₄ branched alkenyl, and C₄ branched alkoyl;

c) X is selected from the group consisting of NR₁, CHR₁, CR₁, O and S, wherein R₁ is selected from the group consisting of:

1) hydrogen;

2) K where K is selected from the group consisting of: C₁-C₆ straight alkyl, C₂-C₆ straight alkenyl, C₁-C₆ straight alkoyl, C₃-C₆ branched alkyl, C₃-C₆ branched alkenyl, and C₄-C₆ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle ~~and a 1-2 ring heterocycle~~, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: -CH₂L and -COCH₂L where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a C₅-C₉ a-amino-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

5) a C₅-C₉ a-amino-w-aza-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon; and

6) a C₅-C₉ a-amino-w-thia-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

d) Z₁ and Z₂ are chosen independently from the group consisting of: =O, -NHR₂, -CH₂R₂, -NR₂OH; wherein Z₁ and Z₂ may not both be =O and wherein R₂ is selected from the group consisting of:

1) hydrogen;

2) K, where K is selected from the group consisting of: C₁-C₆ straight alkyl; C₂-C₆ straight alkenyl, C₁-C₆ straight alkoyl, C₃-C₆ branched alkyl, C₃-C₆ branched alkenyl, and C₄-C₆ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: -CH₂L and -COCH₂L where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a C₄-C₈ a-amino-carboxylic acid attached via the w-carbon;

5) B, wherein B is selected from the group consisting of: -CO₂H, -NHOH, -SO₃H, -NO₂, OP(=O)(OH)(OJ) and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, C₁-C₆ straight alkyl, C₃-C₆ branched alkyl, C₂-C₆ alkenyl, C₃-C₆ branched alkenyl, and aryl, wherein B is optionally connected to the nitrogen via a linker selected from the group consisting of: C₁-C₂ alkyl, C₂ alkenyl, and C₁-C₂ alkoyl;

6) -D-E, wherein D is selected from the group consisting of: C₁-C₃ straight alkyl, C₃ branched alkyl, C₂-C₃ straight alkenyl, C₃ branched alkenyl, C₁-C₃ straight alkoyl, aryl and aroyl; and E is selected from the group consisting of: -(P(=O)₃)_nNMP, where n is 0-2 and NMP is ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; -[P(=O)(OCH₃)(O)]_m-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of

the base; $-\text{P}(=\text{O})(\text{OH})(\text{CH}_2)_m\text{-Q}$, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chosen independently from the group consisting of: Cl, Br, epoxy, acetoxy, $-\text{OG}$, $-\text{C}(=\text{O})\text{G}$, and $-\text{CO}_2\text{G}$, where G is independently selected from the group consisting of: $\text{C}_1\text{-C}_6$ straight alkyl, $\text{C}_2\text{-C}_6$ straight alkenyl, $\text{C}_1\text{-C}_6$ straight alkoyl, $\text{C}_3\text{-C}_6$ branched alkyl, $\text{C}_3\text{-C}_6$ branched alkenyl, $\text{C}_4\text{-C}_6$ branched alkoyl, wherein E may be attached to any point to D , and if D is alkyl or alkenyl, D may be connected at either or both ends by an amide linkage; and

7) $-\text{E}$, wherein E is selected from the group consisting of - $(\text{P}\text{O}_3)_n\text{NMP}$, where n is 0-2 and NMP is a ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-\text{P}(=\text{O})(\text{OCH}_3)(\text{O})_m\text{-Q}$, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; $-\text{P}(=\text{O})(\text{OH})(\text{CH}_2)_m\text{-Q}$, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chose independently from the group consisting of: Cl, Br, epoxy, acetoxy, $-\text{OG}$, $-\text{C}(=\text{O})\text{G}$, and $-\text{CO}=\text{G}$, where G is independently selected from the group consisting of: $\text{C}_1\text{-C}_6$ straight alkyl, $\text{C}_2\text{-C}_6$ straight alkenyl, $\text{C}_1\text{-C}_6$ straight alkoyl, $\text{C}_3\text{-C}_6$ branched alkyl, $\text{C}_3\text{-C}_6$ branched alkenyl, $\text{C}_4\text{-C}_6$ branched alkoyl; and if E is aryl, E may be connected by an amide linkage;

e) if R_1 and at least one R_2 group are present, R_1 may be connected by a single or double bond to an R_2 group to form a cycle of 5 to 7 members;

f) if two R_2 groups are present, they may be connected by a single or a double bond to form a cycle of 4 to 7 members; and

g) if R_1 is present and Z_1 or Z_2 is selected from the group consisting of - NHR_2 , $-\text{CH}_2\text{R}_2$ and $-\text{NR}_2\text{OH}$, then R_1 may be connected by a single or double bond to the carbon or nitrogen of either Z_1 or Z_2 to form a cycle of 4 to 7 members.